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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,746	CHEN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-6 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that 1) It would not be a burden for the Examiner to examine SEQ ID Nos:3-18, which are fragments of SEQ ID NO:2, because these sequences would be found in a search for SEQ ID NO:2, 2) Groups II, IV and V, encompassing the methods of use of the polynucleotides of group I are classified in the same class and subclass, and would therefore involve the same search. Furthermore, the limitation in claim 8 does not represent a separate method of detection. Moreover, since the methods of claims 7-12 also depend from and are of the same scope as the polynucleotides of group I, they could be examined together with group I without undue burden, and 3) The species requirement of groups V and VII misrepresent the concept of election of species. The patentable distinctiveness of the molecules or compounds recited in the claims are not an issue for examination purposes as the claims are to a method of use of the composition of group I and not the species themselves. This is not found persuasive because of the following reasons: 1) The searches for the species SEQ ID Nos: 3-18 require different type of searches than the search for SEQ ID NO:2, and it would be a burden for the Examiner to examine SEQ ID Nos:3-18 together with SEQ ID NO:2, .2) Groups II, IV and V are classified in a different class and subclass than those of group I, which are different from each other as product and process and are not of the same scope, and the searches for these groups are not co-extensive and

therefore, it would be a burden for the Examiner to examine these groups together. Further although Groups II, IV and V are classified in the same class and subclass, the searches for these groups require several different databases and are not just based on classification search, and are not co-extenisve, and therefore, it would be a burden for the Examiner to examine these groups together. Moreover, group III, claim 8, is distinct from group II because group III requires an additional step, amplification of the nucleic acid before hybridization, not found in group II, and the searches for these groups are not co-extensive and therefore, it would be a burden for the Examiner to examine these groups together, and 3) In groups V and VII, the species are used for combining with the polynucleotide of group I to detect specific binding. Since the species are structurally and functionally distinct, the methods of groups V and VII using different species differ in reagents and/or dosages, and/or schedules used, response variables and criteria for success.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-6, SEQ ID NO:2 only and a naturally occurring variant thereof are examined in the instant application. SEQ ID Nos: 3-18 are withdrawn from consideration as being drawn to non-elected species.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 1-6 are drawn to 1) the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, or complement thereof, or a naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2 or the complement thereof, 2) a composition comprising said nucleic acid sequence and a labeling moiety, 3) a vector comprising said nucleic acid sequence, a host cell comprising said vector, and 4) a method for using a cDNA to produce a protein.

The disclosed utilities for SEQ ID NO:2 or MRTM (mucine related tumor marker) include diagnosis and treatment of cancer, in particular breast cancer, production of and screening of antibodies that specifically bind to SEQ ID NO:2 (p.16-23). However, neither the specification nor any art of record teaches what SEQ ID NO:2 is, what it does do, they do not teach a utility for any of the fragments or the derivatives claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

The asserted utilities for SEQ ID NO:2, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered specific utilities, i.e. they are not specific to SEQ ID NO:2. Additional disclosed utilities for SEQ ID NO:2 include therapy and diagnosis of cancer, in particular breast cancer. The asserted utility of SEQ ID NO:2 is based on the assertion that SEQ ID NO:1, encoded by SEQ ID NO:2 has chemical and structural homology to mucin proteins, and that in particular SEQ ID NO:1 and human mucin MUC3 and porcine gastric mucine PGM-9B share 26% identity (p.10, second paragraph bridging p. 11 and figure 2). In addition, SEQ ID NO:1 has a biologically active portion extending from C594 to C627. Further, SEQ ID NO:1 has 13 potential N-glycosylation sites, several potential phosphorylation sites, one potential aspartic acid and asparagines hydroxylation iste, one potential EGF-1-like domain signature, one potential EGF-2-like domain signature, two potential calcium-binding EGF-like domain signatures, and a predicted transmembrane segment (p.10). By Northern analysis, SEQ ID NO:2 is overexpressed in breast cancer cell line BT20 as compared to normal cells (table 1 on p.40). The specification discloses that cell lines derived from human mammary epithelial cells at various stages of breast cancer provide a useful model to study the process of malignant transformation and tumor progression, as it has been shown by Wistuba et al, 1998, Clinical Cancer Res, 4: 2931-2938,

that these cell lines retain many of the properties of their parental tumors for lengthy culture periods (specification, p.2, paragraph before last).

It is noted that the specification does not disclose any biological activity of SEQ ID NO:1, nor any data confirming that the portion extending from C594 to C627 of SEQ ID NO:1 has any biological activity, nor consensus sequences required for the activity of the encoded protein or for the identification of a mucin protein. It is clear that, although there is a 26% identity between human mucin MUC3 and porcine gastric mucine PGM-9B and SEQ ID NO:1, there is a 74% dissimilarity between SEQ ID NO:1 and human mucin MUC3 and porcine gastric mucine PGM-9B; and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional

structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 74% dissimilarity to human mucin MUC3 and porcine gastric mucine PGM-9B, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with human mucin MUC3 and porcine gastric mucine PGM-9B, nor would it be expected to be the same as that of human mucin MUC3 and porcine gastric mucine PGM-9B In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398,

col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane

protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter downregulated in adenoma. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 74% dissimilarity to human mucin MUC3 and porcine gastric mucine PGM-9B, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with human mucin MUC3 and porcine gastric mucine PGM-9B, nor would it be expected to be the same as that of human mucin MUC3 and porcine gastric mucine PGM-9B. Further, even if SEQ ID NO:1 is a human mucin MUC3 and porcine gastric mucine PGM-9B -like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, does not

teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or which derivatives would function as claimed in a pharmaceutical composition.

Moreover, although the specification discloses overexpression of SEQ ID NO:2 in a breast cancer cell line BT20 as compared to normal cells, and although Wistuba et al teach that cell lines recited in table 2 on page 2936 retain many of the properties of their parental tumors for culture periods up to 60 months, the cell lines studied by Wistuba et al are specific cell lines that are cultured from a subset of primary breast carcinomas that have several features indicative of advanced tumors with poor prognosis, whereas it seems that the cell line BT20 studied in the claimed invention is not from the same subset of primary breast carcinoma and is not the same as the cell lines studied by Wistuba et al. Thus it is unpredictable that the cell line BT20 has any of the properties of the cell lines studied by Wistuba et al, and retain many of the properties of their parental tumors for culture periods up to 60 months. Further, the period of culture of the cell lines studied by Wistuba et al during which the retention of the parental tumors are retained is only up to 60 months. It is not clear how long the cell line BT20 has been in culture, especially it is well known in the art that cell lines could have been in culture for years and years.

In addition, it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor.

Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Mustafa O et al, 1996, Intl J Oncology, 8(5): 883-888, teach that prostate cells in late culture all show numerous changes in chromosome 5 in addition to some new markers. The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data

received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex

conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that the cell line BT20 could represent the parental breast cancer, and that overexpression of SEQ ID NO:2 in the cell line BT20 could be correlated with overexpression of SEQ ID NO:2 in primary breast cancers.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 1-6 are drawn to 1) the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, or "complement" thereof, or a "naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2" or the "complement "thereof, 2) a composition comprising said nucleic acid sequence or the complement thereof and a labeling moiety, 3) a vector comprising said nucleic acid sequence, a host cell comprising said vector, and 4) a method for using a cDNA to produce a protein.

It is noted that a complement could be partial or complete complement, wherein partial complement could share with SEQ ID NO:2 only a few common nucleotides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*. (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:16, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606,

(CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties , not a mere wish or plan for obtaining the claimed chemical invention .

Support for allelic variants is provided in the specification on page 9, lines 13-9, where it is disclosed that the invention encompasses allelic variants that have high percent identity with SEQ ID NO:2, and may differ by about three bases per hundred base, and on page 11, wherein it is disclosed that the invention encompasses variants having at least 80%, 90% or 95 % identity to SEQ ID NO:2. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides.

The claims read on polynucleotide variants of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:2. The specification and the claims do not place any limit on which amino acid that is subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural polynucleotide variants, and nucleotide sequences encoding numerous structural variants. The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) that are naturally substituted, or to which type of substitution besides conservative substitution, or which amino acids that are naturally deleted or inserted so that the claimed polypeptide could function as contemplated. Structural features, that could distinguish the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants from the nucleotide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are

disclosed. In addition, no common functional attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138).

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 1, 4-6 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide of SEQ ID NO:2, does not reasonably provide enablement for a polynucleotide encoding SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 4-6 are drawn to a polynucleotide "encoding" SEQ ID NO:1, a vector comprising said polynucleotide, a host cell comprising said vector, and a method of making a protein.

The specification discloses isolation of SEQ ID NO:2 which is overexpressed in a breast cancer cell line. There is no evidence that the deduced SEQ ID NO:1 is expressed in any tissue. One cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching of whether any protein product is actually produced. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any

concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:2 is translated into a polypeptide expression product.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 101 and 112, first paragraph rejection, claim 2 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for variants of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 2 is drawn a naturally occurring polynucleotide sequence having at least 90% sequence identity with SEQ ID NO:2.

Applicants have not shown how to make and use the claimed variant polynucleotides, and nucleotide sequences encoding the polypeptide variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) are naturally subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

3. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 1-6 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for a "complement" of SEQ ID NO:2, or a nucleic acid sequence encoding SEQ ID NO:1 or a naturally occurring variant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-6 are drawn to 1) the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, or "complement" thereof, or a "naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2" or the "complement" thereof, 2) a composition comprising said nucleic acid

sequence or the "complement" thereof and a labeling moiety, 3) a vector comprising said nucleic acid sequence, a host cell comprising said vector, and 4) a method for using a cDNA to produce a protein.

It is noted that a complement could be partial or complete complement, wherein partial complement could share with SEQ ID NO:2 only a few common nucleotides.

The claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to SEQ ID NO:2, that is polynucleotides that are complement to SEQ ID NO:2, or a nucleic acid sequence encoding SEQ ID NO:1 or a naturally occurring variant thereof. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:2.

In view of the above, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2 are rejected under 35 USC 102(b) as being anticipated by Nagase T et al, Genbank Sequence Database (Accession AB033063), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 1999 or PN=5,849578.

Claims 1-2 are drawn to a "complement" of the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, and a "naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2" or the "complement" thereof

Nagase et al teach a polynucleotide which is 100% similar to SEQ ID NO:2, from nucleotide number 1533 to 6674, according to sequence similarity search (MPSRCH search report, 2002, us-09-840-746-2.rge, pages 1-4).

PN=5,849578 teaches a polynucleotide (SEQ ID NO:7) which is 94% similar to SEQ ID NO:2, from nucleotide number 1 to 5441, according to sequence similarity search (MPSRCH search report, 2002, us-09-840-746-2.rni pages 1-4).

Given the polynucleotide sequence taught by Nagase et al or PN=5,849578, one of ordinary skill in the art would immediately envision the claimed polypeptide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

September 29, 2002

SUSAN UNGAR
Primary Patent Exr